SUPPLEMENTAL TABLES AND FIGURES

Table S1, related to Figure 2. FreeSurfer ROIs included in Braak stage ROIs

Braak stage	FreeSurfer-derived ROIs
I	Entorhinal cortex
II	Hippocampus
III	Parahippocampal gyrus; fusiform gyrus; lingual gyrus; amygdala
IV	Inferior temporal cortex; middle temporal cortex; temporal pole; thalamus; caudal, rostral, isthmus, posterior cingulate; Insula
V	Frontal cortex; parietal cortex; occipital cortex; transverse, superior temporal cortex; precuneus; banks of superior temporal sulcus; nucleus accumbens; caudate nucleus; putamen
VI	Precentral gyrus; postcentral gyrus; paracentral gyrus; cuneus; pericalcarine

A detailed ROI list with FreeSurfer lookup table numbers for Braak ROIs is available at http://jagustlab.neuro.berkeley.edu/research.html.

Table S2, related to Figure 2. Group classification pre- and post-PVC

	Pre-PVC effect size	p	Post-PVC effect size	p
Braak I/II	0.92	.001	0.95	.001
Braak III/IV	0.99	.001	1	.001
Braak V/VI	0.96	.001	0.97	.001

Mann-Whitney U test (OA vs. AD, Common Language Effect Size).

Table S3, related to Figure 5. Episodic memory and AV-1451 associations

A MNI coordinates of significant negative associations between cross-sectional episodic memory and AV-1451 ($p < .005$ uncor., k > 100)

Voxels (n)	X	Y	Z	Region(s)
313	59	52	23	L anterior parahippocampal gyrus (entorhinal cortex), posterior parahippocampal gyrus, hippocampus
130	35	57	25	R anterior parahippocampal gyrus (entorhinal cortex), posterior parahippocampal gyrus, hippocampus

B MNI coordinates of significant negative associations between retrospective longitudinal episodic memory and AV-1451 ($p < .005$ uncor., k > 100)

| Voxels (n)	X	Y	Z	Region(s)
300	58	58	19	L anterior parahippocampal gyrus (entorhinal cortex), posterior parahippocampal gyrus, hippocampus
262	32	59	18	R anterior parahippocampal gyrus (entorhinal cortex), posterior parahippocampal gyrus, hippocampus

Table S4, related to Figure 6. Age, PiB, and AV-1451 associations

A MNI coordinates of significant positive associations between Age (controlling for PiB) and AV-1451 (*p* < .005 uncor., k > 100)

| Voxels (n)	X	Y	Z	Region(s)
2293	33	61	17	R Anterior parahippocampal gyrus (entorhinal cortex)
1500	47	67	29	L Subcallosal cortex (ventral frontal)
1446	38	38	35	R Posterior parahippocampal gyrus/lingual gyrus
597	54	36	33	L Posterior parahippocampal gyrus, L anterior parahippocampal gyrus

B MNI coordinates of significant positive associations between PiB (controlling for age) and AV-1451 (*p* < .005 uncor., k > 100)

Voxels (n)	X	Y	Z	Region(s)
2423	32	50	23	R Posterior parahippocampal gyrus
2394	61	48	23	L Fusiform cortex/posterior parahippocampal gyrus
297	72	67	30	L Superior temporal gyrus (anterior)
178	19	69	32	R Superior temporal gyrus (anterior)
136	13	62	38	R Superior temporal gyrus (anterior)

**Figure S1, related to Figure 2.** PVC effect on selected ROIs
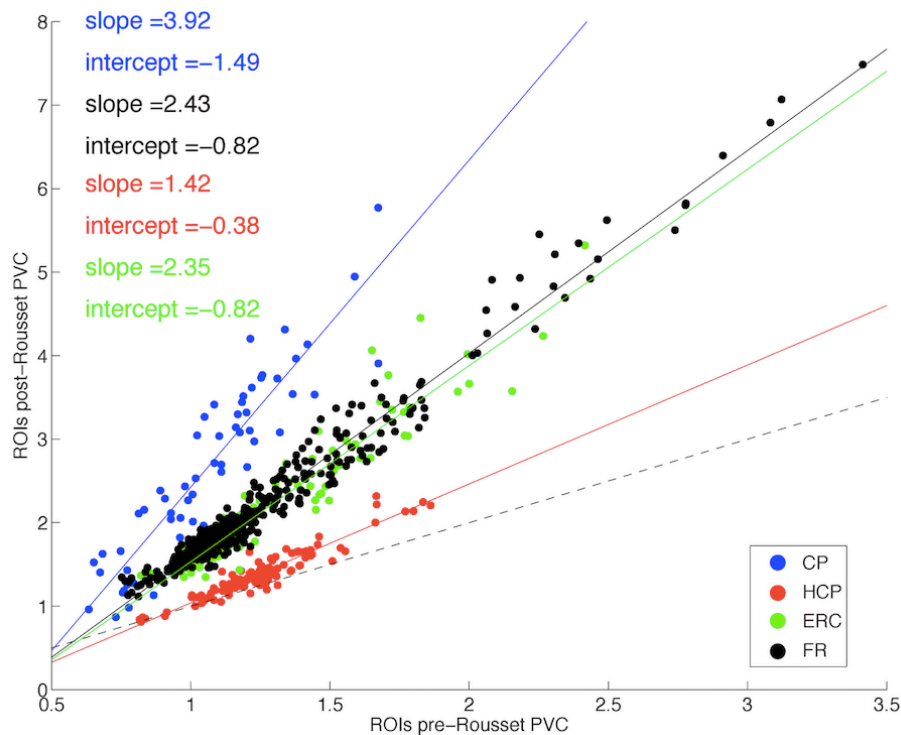
Mean unilateral ROI AV-1451 signal for n = 53 participants, before (x axis) and after (y axis) Rousset partial volume effect correction (PVC). Post-correction signal increases relative to pre-correction signal (dotted line = unity), a property of PVC methods. Fits of linear regression models for each ROI are presented in text: CP (blue) = Choroid plexus; HCP (red) = Hippocampus; ERC (green) = Entorhinal cortex; FR (black) = Frontal cortex.

**Figure S2, related to Figure 3.** Conditional reference-tree regression model for *in vivo* Braak staging
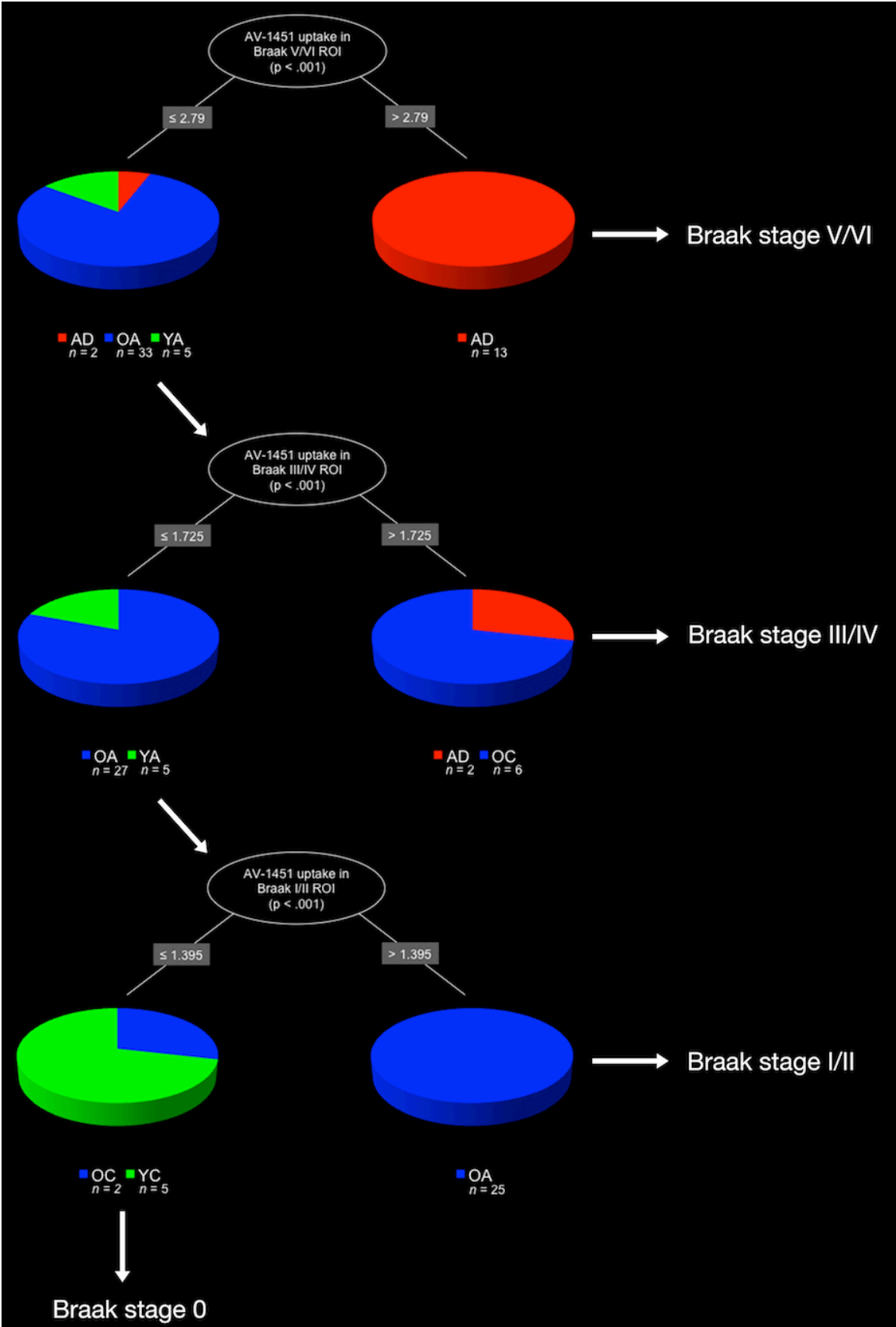
Conditional inference tree results were used to classify AD, OA, and YA participants into Braak stages based on AV-1451 uptake in Braak stage ROIs.

Figure S3, related to Figure 4. Relationship of PiB uptake (amyloid) with change in global cognition in OA
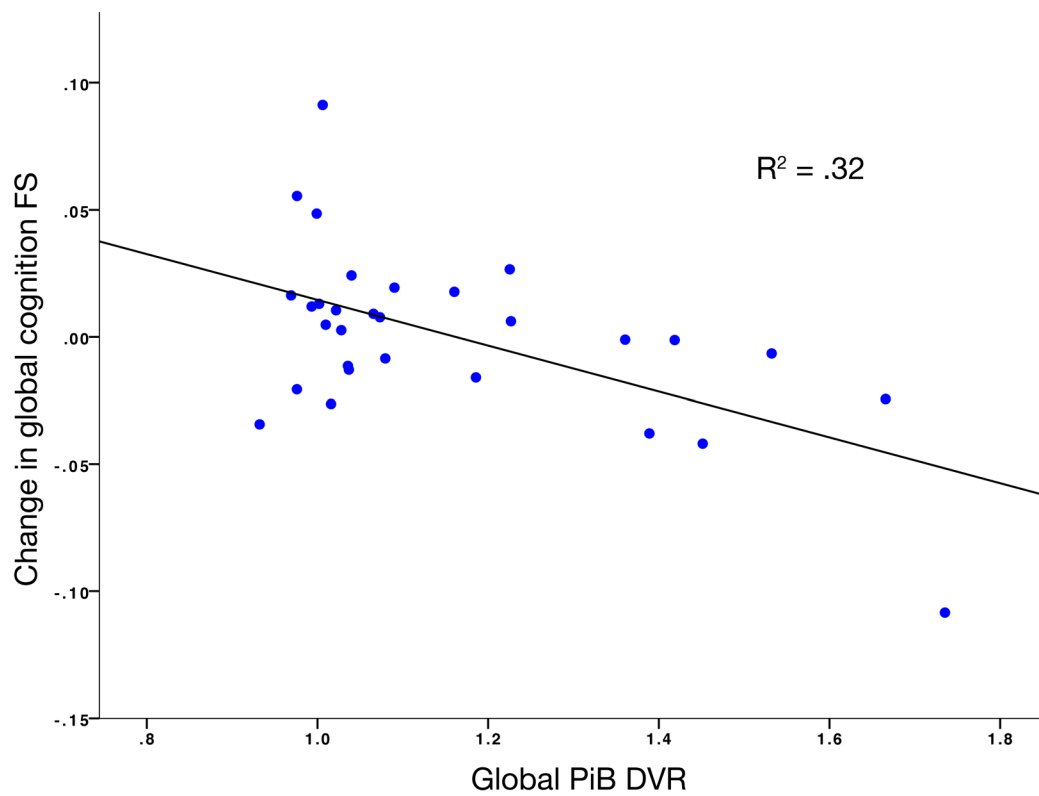

Global PiB DVR (x axis) vs. slope in retrospective longitudinal global cognition (y axis) for n = 30 OA.

Figure S4, related to Figure 6. Age vs. PiB in OA (*n* = 33)
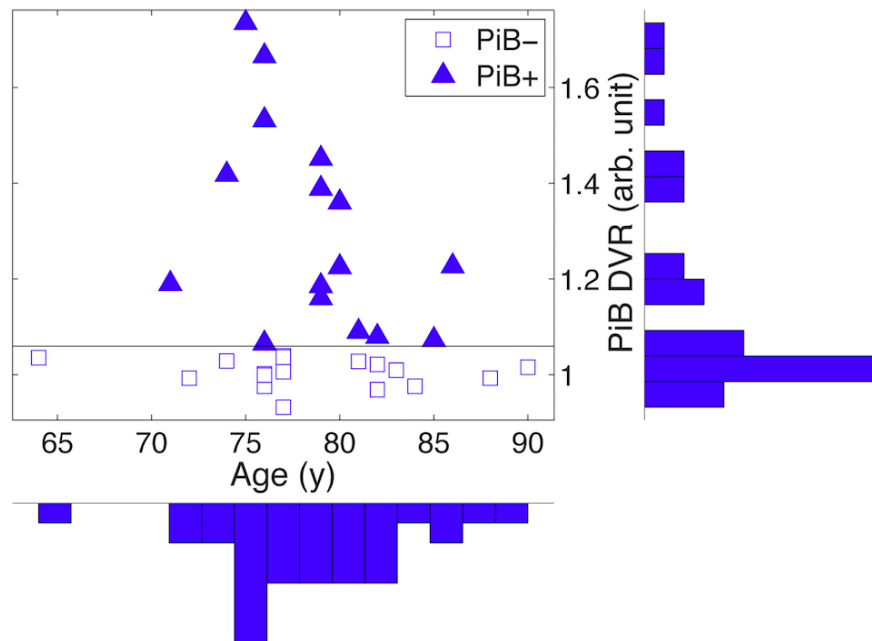

Chronological age (years, x axis) and PiB global DVR (y axis) for n = 33 cognitively healthy elderly. Participants are also identified by PiB status (>=1.06).

**Figure S5, related to Figures 4 and 5.** Patterns of longitudinal cognitive change in OA (*n* = 30)
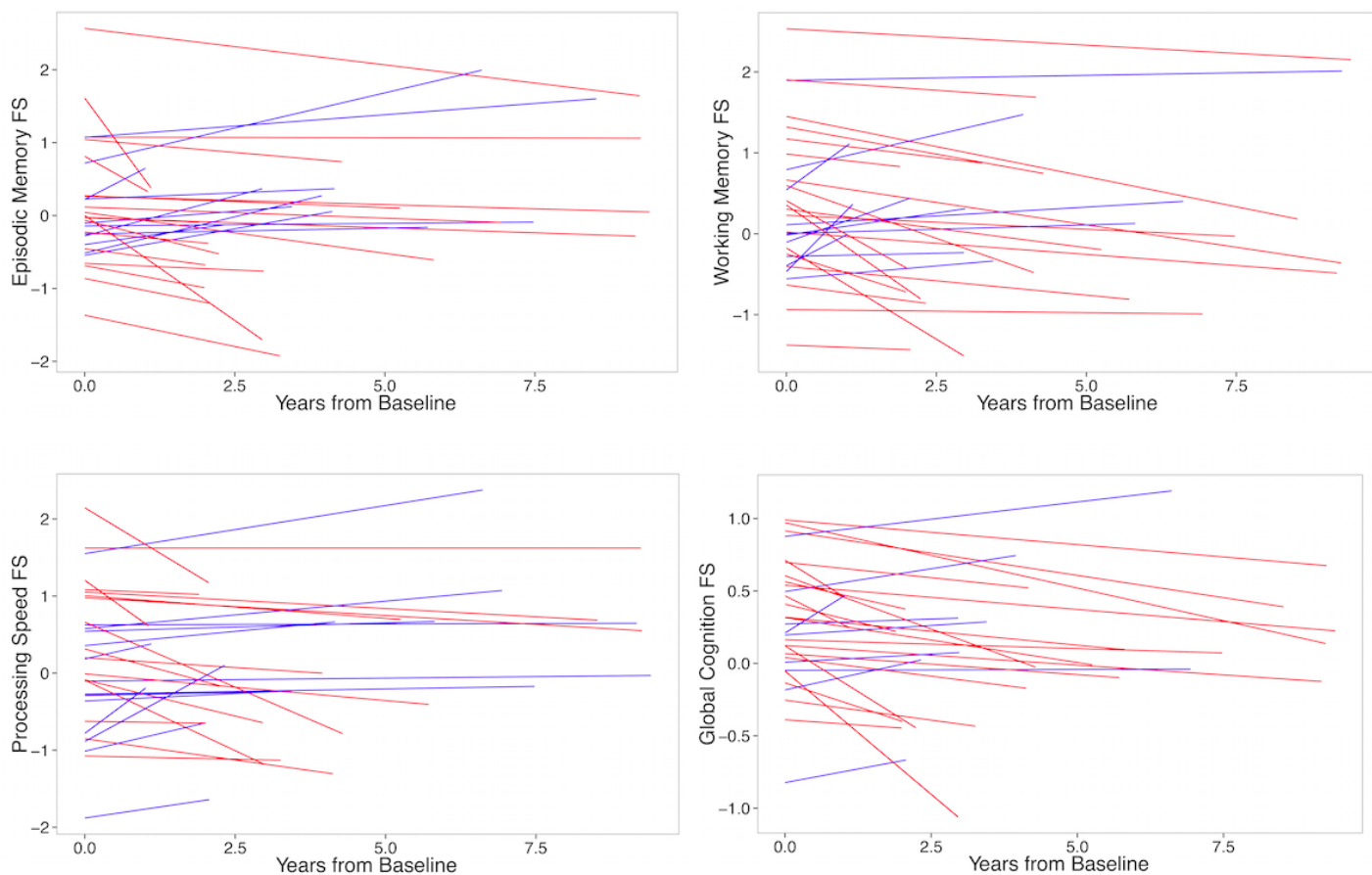
Trajectories of retrospective longitudinal cognitive change for n = 30 OA for cognitive factor domains. Different colors represent OA participants exhibiting decline (red) or improvement (blue) over time.
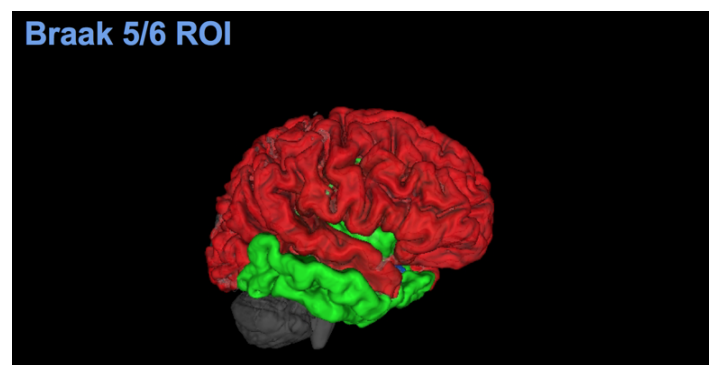
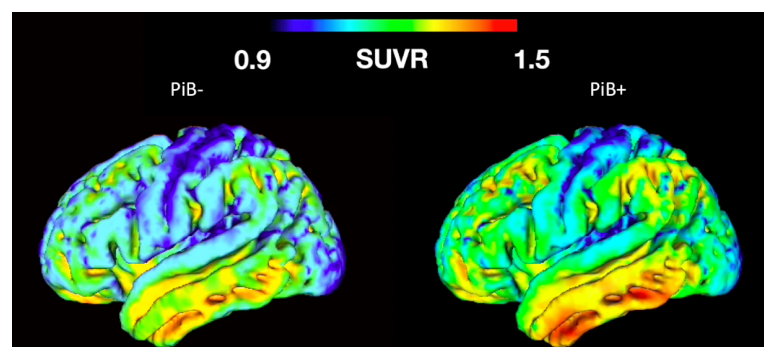**Movie S1, related to Figure 2.** Braak stage I/II ROI
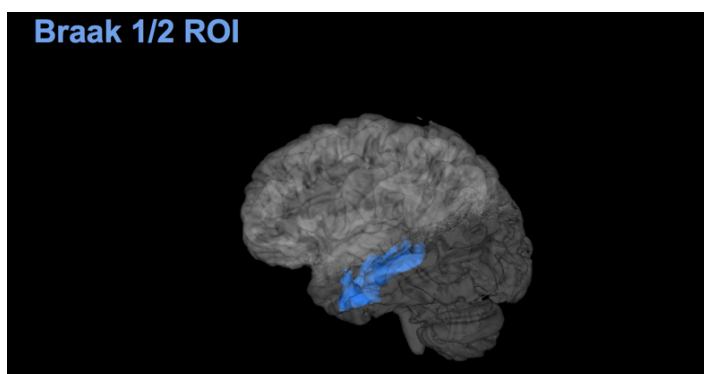
Movie S2, related to Figure 2. Braak stage III/IV ROI
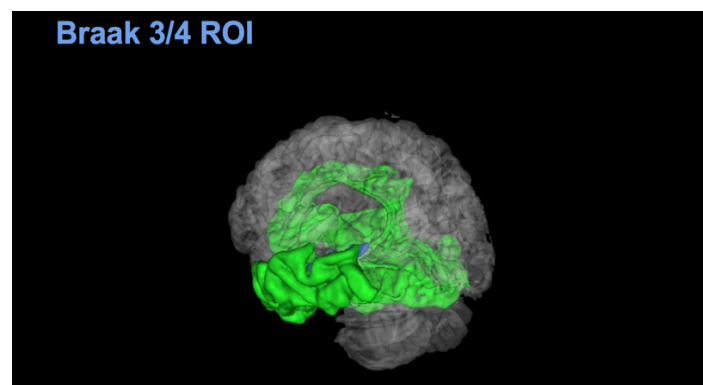
Movie S3, related to Figure 2. Braak stage V/VI ROI

Movie S4, related to Figure 6. Older adult AV-1451 patterns by PiB status

Three-dimensional, rotating views of lateral cortical AV-1451 update for PiB- (left) and PiB+ (right) healthy elderly.

SUPPLEMENTAL EXPERIMENTAL PROCEDURES

Participants: BACS participant eligibility requirements and neuropsychological examination
We recruited 33 cognitively healthy older adults (OA) and five cognitively healthy young adults from the Berkeley Aging Cohort Study (BACS). BACS eligibility requirements included no imaging contraindications, community-dwelling, Mini-Mental State Examination (MMSE) score ≥ 26, normal performance on cognitive tests (within 1.5 SD of normative values on the California Verbal Learning Test [Delis et al. 2000] and Delayed Recall from the Wechsler Memory Scale [Wechsler 1997]), absence of neurological or psychiatric illness, and lack of major medical illnesses and medications that affect cognition. All cognitively healthy OA were defined as cognitively normal upon BACS study entry, and all OA participants remained defined as cognitively normal at the time of the study (all cognitive time points).

Participants: AD sample recruitment strategy
The AD sample studied here (one participant diagnosed with behavioral/dysexecutive variant of AD, one with early-onset amnestic AD, three as late-onset amnestic AD, four with logopenic variant primary progressive aphasia, and six with posterior cortical atrophy) clinically does not represent a typical group of primarily late-onset amnestic AD. However, our goal in the current study was to provide data representative of high, clinical levels of tau pathology for the AV-1451 Braak staging procedure to be able to identify thresholds, and as thus we included a variety of AD phenotypes in the AD participant sample.

***In vivo* Braak staging data preprocessing: Partial volume correction (PVC)**
We applied PVC to our native-space AV-1451 dataset, following procedures described in Rousset et al. (1998). This processing step was done to control for effects of tracer spill-in and spill-out on native space ROI data and results; an examination of Rousset PVC for template space image data is beyond the scope of this manuscript. Application of PVC to native-space ROI data did not substantially affect results. As there is no standard accepted PVC method for AV-1451 PET, these methods and results were considered exploratory and methods development. Our ROI-staging system balanced number of ROIs with expected spatial variability of AV-1451 signal. For example, as signal could vary across temporal subregions and hemispheres, multiple bilateral temporal regions were included (see Table S1). FreeSurfer-generated ROIs were used to define regions including cortical and subcortical brain structures described in Table S1, as well as remaining brain structures with non-zero AV-1451 signal, including white matter and choroid plexus. As choroid plexus ROIs were most often adjacent to hippocampus, we manually checked segmentations of both structures, and assessed the impact of PVC on hippocampal and choroid plexus signals (Figure S1). Comparison of signal between choroid plexus (high slope), regions distant from choroid plexus (frontal cortex, middle slope), and regions adjacent to choroid plexus (hippocampus, lower slope) suggest that choroid plexus modeling may aid in the estimation of true signal in adjacent regions such as hippocampus.

Neuropsychological examination: Cognitive factor score generation
For each testing session, factor scores were calculated for episodic memory, working memory, and executive function/processing speed domains using a maximum likelihood estimation (MLE; Bentler and Kano, 1990) analysis adjusted for test results from a larger sample of 346 BACS participants (further analyses of cognitive factor scores are the topic of a separate manuscript). The participants used in factor score generation were on average 74.6 years old (SD = 7.0), 65.3% female, with an average of 16.7 years (SD = 2.2) education and a mean MMSE score of 28.6 (SD = 1.5). Cognitive data for factor score generation included 87 scores from 19 different tests administered to all 346 participants during assessments. MLE factor analysis was used to reduce data dimensionality and extract latent variables consistent with cognitive models. Cognitive tests were carefully chosen for factor score generation by ensuring variables were normally distributed but not excessively collinear ($r < .7$), with minimal data loss (data present for > 90% of total sample); this yielded 14 cognitive tests for factor analysis. The final solution (three factors) demonstrated significant goodness-of-fit ($\chi2 = 67.85$, df = 42, $p < .01$, RMSEA < 0.05), explaining 56% of total model variance. Factor 1 was interpreted as episodic memory and was comprised of the California Verbal Learning Test (Delis et al., 2000) total number of words recalled across five learning trials, WMS-III Logical Memory Story A+B1 Free Recall and Visual Reproduction Long Delay (Wechsler, 1997), Listening Span (Daneman and Carpenter, 1980) total number of words recalled, and Category Fluency total number of animals and vegetables (Spreen and Benton, 1977). Additional factors were interpreted as Working Memory, made up of WMS-III Digit Span test forward and backwards, and Arithmetic tasks (Wechsler, 1997); and Processing Speed/Executive Function, composed of the Digit-Symbol test (Smith, 1982), Stroop Interference Test (number correct in 60 sec; Stroop, 1938), WMS-III Mental Control test (Wechsler, 1997), Trails A, and taps per second on a finger tapping task (Reitan and Wolfson, 1985). Factor scores were generated by z-scoring each variable and, for each participant, multiplying the value by the MLE-derived weight specific to that variable for each factor. A global cognition measure was also created by averaging the three factor scores.

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